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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,013	04/04/2006	Rudolf Fahrig	P28506	8056

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EXAMINER	
HENRY, MICHAEL C	
ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
09/19/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
pto@gbpatent.com

Office Action Summary	Application No.	Applicant(s)	
	10/550,013	FAHRIG ET AL.	
	Examiner	Art Unit	
	MICHAEL C. HENRY	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-12,16 and 17* is/are rejected.

7)☐ Claim(s) *13-15 and 18-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The following office action is a responsive to the Amendment filed, 06/18/08.

The amendment filed 06/18/08 affects the application, 10/550,013 as follows:

1. Claims 8-10 been amended. The rejections made under 35 U.S.C. 103(a) in the prior office action mailed 03/18/08 are maintained.
2. The responsive to applicants' arguments is contained herein below.

Claims 8-26 are pending in application

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-12, 16, 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fahrig et al. (WO 96/23506, English Translation).

In claim 8, applicant claims a method of increasing apoptotic effect of cytostatics after chemotherapy comprising administering a 5-substituted nucleoside comprising (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), salt, prodrug or mixture thereof, the administering being without administration of a cytostatic, during a recovery phase after a cytostatic chemotherapy cycle. Claim 9 is drawn to said method wherein the administration includes cytostatic and a 5-substituted nucleoside comprising BVDU, a protected form, salt prodrug, or mixture thereof. Claims 10-12, 16, 17 are drawn to said method involving the administration of specific amounts

of cytostatic and BVDU, specific recovery phase and chemotherapy cycle, and specific concentration of 5-substituted nucleoside in the blood and specific cytostatics.

Fahrig et al. disclose that 5'substituted nucleosides in combination with at least one cytostatic can be used in the production of a medicament to prevent or reduce the build-up of resistance in cytostatic treatment and a medicament containing BVDU and/or its metabolites (see abstract). It should be noted that the apoptotic effect encompasses the cytostatic treatment disclosed by Fahrig et al. Furthermore, Fahrig et al. disclose that BVDU alone appears slightly to lessen the spontaneous degree of gene amplification (see page 10- line 24 to page 11, line 3). In addition, Fahrig et al. disclose that BVDU, in clinically relevant doses, inhibits AMP-induced gene amplification and that the said inhibition is dose dependent (see page 10- line 24 to page 11, line 3). This implies that BVDU has the effect of preventing or reducing the build-up of resistance resulting from cytostatic treatment.

The difference between applicant's claimed method and the method suggested by Fahrig et al. is that Fahrig et al. do not disclose administering said BVDU during the recovery phase after a cytostatic chemotherapy cycle. However, Fahrig et al. suggest that BVDU can cause the apoptotic effect of the cytostatic to be more effective (i.e., increased) due to the build-up of resistance in cytostatic treatment. This implies that BVDU has the effect of preventing or reducing the build-up of resistance resulting from cytostatic treatment. Consequently, a skilled artisan would be motivated to administer BVDU alone to reduce the build-up of resistance resulting from cytostatic treatment and to exclude the administration of more cytostatic which may cause side effects or adverse effects and to optimize or maximize the effectiveness of said cyotostatic especially during a recovery phase after a cytostatic chemotherapy cycle.

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made in view of Fahrig et al., to increase apoptotic effect of cytostatics after chemotherapy comprising administering said BVDU, during a recovery phase after a cytostatic chemotherapy cycle based on factors such as the severity of the build-up of resistance due to the cytostatic treatment (especially after chemotherapy cycle), the side effects or adverse effects of excess cytostatics build up, the maximum tolerant dose of the cytostatic and the type of individual treated, since Fahrig et al. disclose that BVDU and/or its metabolites can reduce the build-up of resistance in cytostatic treatment.

One having ordinary skill in the art would have been motivated, in view of Fahrig et al. to increase apoptotic effect of cytostatics after chemotherapy comprising administering said BVDU, during a recovery phase after a cytostatic chemotherapy cycle based on factors such as the severity of the build-up of resistance in cytostatic treatment (especially after chemotherapy cycle), the side effects or adverse effects of excess cytostatics, the tolerant dose of the cytostatic and the type of individual treated, since Fahrig et al. disclose that BVDU and/or its metabolites can reduce the build-up of resistance in cytostatic treatment. It should be note that the use of specific ratios of drugs, agents or cytostatics and frequency of administration depends on factors such as the type and severity of the condition treated and the kind of subject treated.

Allowable Subject Matter

Claims 13-15, 18-26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The method of claims 13-15, 18-26 possess differences to the method of prior art documents and these differences are not suggested in the prior art, nor are

obvious over the prior art. For example, the method of claims uses compounds that are different to the compounds of prior art.

Response to Arguments

Applicant's arguments with respect to claims 8-12, 16, 17 have been considered but are not found convincing.

The applicant argues that reduction in gene amplification is not an indication for spontaneous apoptosis, but is just an explanation for an enhanced take-up of cytostatics. That is, a reduction in gene amplification indicates that cytostatic agents will not be shuttled out of the cells as efficiently, thereby making the cytostatic agent more effective *when the cytostatic agent is present in the cell.* However, Fahrig et al. disclose that BVDU alone appears slightly to lessen the spontaneous degree of gene amplification (see page 10- line 24 to page 11, line 3). In addition, Fahrig et al. disclose that BVDU, in clinically relevant doses, inhibits AMP-induced gene amplification and that the said inhibition is dose dependent (see page 10- line 24 to page 11, line 3). This implies that BVDU has the effect of preventing or reducing the build-up of resistance resulting from cytostatic treatment. Furthermore, the reduction in gene amplification means enhanced take-up of cytostatics (or reduction in the build-up of resistance) and consequently an increase or enhanced apoptosis effect or cytostatic treatment. In addition, the reduction in the shuttling of the cytostatic agent out of the cell due to the reduction or inhibition of spontaneous degree of gene amplification promotes, increases or enhances the apoptosis or cytostatic treatment.

The applicant argues that the portion of the Fahrig PCT cited in the Office Action (page 10, line 24 to page 11, line 3) only serves as an explanation of the efficacy of a 5'

substituted nucleoside in the presence of a cytostatic agent - it does not explain, or even suggest, the increased apoptosis observed when a 5' substituted nucleoside is administered during a recovery phase after a cytostatic chemotherapy cycle. On the contrary however, Fahrig et al. disclose that BVDU alone appears slightly to lessen the spontaneous degree of gene amplification (see page 10- line 24 to page 11, line 3). In addition, Fahrig et al. disclose that BVDU, in clinically relevant doses, inhibits AMP-induced gene amplification and that the said inhibition is dose dependent (see page 10- line 24 to page 11, line 3). This suggests that BVDU when used alone also can prevent or reduce the build-up of resistance resulting from cytostatic treatment. Furthermore, the reduction in gene amplification means enhanced take-up of cytostatics (or reduction in the build-up of resistance) and consequently an increase or enhanced apoptosis effect or cytostatic treatment. In addition, the reduction in the shuttling of the cytostatic agent out of the cell due to the reduction or inhibition of spontaneous degree of gene amplification promotes, increases or enhances the apoptosis or cytostatic treatment.

The applicant argues that because of the inhibitory effect that 5' substituted nucleosides have on gene amplification (i.e., on shuttling cytotoxic agents out of cancer cells), one of ordinary skill in the art would have expected such compounds not to have any significant effect if administered during a recovery phase after a cytostatic chemotherapy cycle. On the contrary however, based on the teaching of WO 96/23506 those of skill in the art would expect the administration of 5'substituted nucleoside during a recovery phase would be effective in that it would further facilitate the incorporation of cytostatics into the cells depending factors such as on the amount of cytostatic that is built up during the recovery phase after a cytostatic chemotherapy cycle and the rate at which said cytostatic is incorporated into the cells.

Furthermore, the reduction in gene amplification means enhanced take-up of cytostatics (or reduction in the build-up of resistance) and consequently an increase or enhanced apoptosis effect or cytostatic treatment. In addition, the reduction in the shuttling of the cytostatic agent out of the cell due to the reduction or inhibition of spontaneous degree of gene amplification promotes, increases or enhances the apoptosis or cytostatic treatment.

The applicant argues that the present application presents the surprising discovery that administration of a 5' substituted nucleoside during a recovery phase unexpectedly provides better chemotherapeutic results than where there is no such administration during the recovery phase. However, one of ordinary skill would expect that the administration of a 5' substituted nucleoside during a recovery phase would provide better chemotherapeutic results than where there is no such administration during the recovery phase based and since Fahrig et al. disclose that BVDU and/or its metabolites can reduce the build-up of resistance in cytostatic treatment on the teaching Fahrig et al. (see above rejections). It should be noted that the unexpected results presented by applicant was not obtained for the instant invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael C. Henry
September 14, 2008.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner
Art Unit 1623